Stem Cell and Aging Research Literatures

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Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
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1. Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Asumda, F. Z. "Age-associated changes in the ecological niche: implications for mesenchymal stem cell aging." Stem Cell Res Ther. 2013 May 14;4(3):47. doi: 10.1186/scrt197.

Adult stem cells are critical for organ-specific regeneration and self-renewal with advancing age. The prospect of being able to reverse tissue-specific post-injury sequelae by harvesting, culturing and transplanting a patient's own stem and progenitor cells is exciting. Mesenchymal stem cells have emerged as a reliable stem cell source for this treatment modality and are currently being tested in numerous ongoing clinical trials. Unfortunately, the fervor over mesenchymal stem cells is mitigated by several lines of evidence suggesting that their efficacy is limited by natural aging. This article discusses the mechanisms and manifestations of age-associated deficiencies in mesenchymal stem cell efficacy. A consideration of recent experimental findings suggests that the ecological niche might be responsible for mesenchymal stem cell aging.

Baines, H. L., D. M. Turnbull, et al. "Human stem cell aging: do mitochondrial DNA mutations have a causal role?" Aging Cell. 2014 Apr;13(2):201-5. doi: 10.1111/acel.12199. Epub 2014 Jan 28.

A decline in the replicative and regenerative capacity of adult stem cell populations is a major contributor to the aging process. Mitochondrial DNA (mtDNA) mutations clonally expand with age in human stem cell compartments including the colon, small intestine, and stomach, and result in respiratory chain deficiency. Studies in a mouse model with high levels of mtDNA mutations due to a defect in the proofreading domain of the mtDNA polymerase gamma (mtDNA mutator mice) have established causal relationships between the accumulation of mtDNA point mutations, stem cell dysfunction, and premature aging. These mtDNA mutator mice have also highlighted that the consequences of mtDNA mutations upon stem cells vary depending on the tissue. In this review, we present evidence that these studies in mice are relevant to normal human stem cell aging and we explore different hypotheses to explain the tissue-specific consequences of mtDNA mutations. In addition, we emphasize the need for a comprehensive analysis of mtDNA mutations and their effects on cellular function in different aging human stem cell populations.

Beerman, I., C. Bock, et al. "Proliferation-dependent alterations of the DNA methylation landscape underlie hematopoietic stem cell aging." Cell Stem Cell. 2013

Apr 4;12(4):413-25. doi: 10.1016/j.stem.2013.01.017. Epub 2013 Feb 14.

The functional potential of hematopoietic stem cells (HSCs) declines during aging, and in doing so, significantly contributes to hematopoietic pathophysiology in the elderly. To explore the relationship between age-associated HSC decline and the epigenome, we examined global DNA methylation of HSCs during ontogeny in combination with functional analysis. Although the DNA methylome is generally stable during aging, site-specific alterations of DNA methylation occur at genomic regions associated with hematopoietic lineage potential and selectively target genes expressed in downstream progenitor and effector cells. We found that age-associated HSC decline, replicative limits, and DNA methylation are largely dependent on the proliferative history of HSCs, yet appear to be telomere-length independent. Physiological aging and experimentally enforced proliferation of HSCs both led to DNA hypermethylation of genes regulated by Polycomb Repressive Complex 2. Our results provide evidence that epigenomic alterations of the DNA methylation landscape contribute to the functional decline of HSCs during aging.

Beerman, I. and D. J. Rossi "Epigenetic regulation of hematopoietic stem cell aging." Exp Cell Res. 2014 Dec 10;329(2):192-9. doi: 10.1016/j.yexcr.2014.09.013. Epub 2014 Sep 28.

Aging is invariably associated with alterations of the hematopoietic stem cell (HSC) compartment, including loss of functional capacity, altered clonal composition, and changes in lineage contribution. Although accumulation of DNA damage occurs during HSC aging, it is unlikely such consistent aging phenotypes could be solely attributed to changes in DNA integrity. Another mechanism by which heritable traits could contribute to the changes in the functional potential of aged HSCs is through alterations in the epigenetic landscape of adult stem cells. Indeed, recent studies on hematopoietic stem cells have suggested that altered epigenetic profiles are associated with HSC aging and play a key role in modulating the functional potential of HSCs at different stages during ontogeny. Even small changes of the epigenetic landscape can lead to robustly altered expression patterns, either directly by loss of regulatory control or through indirect, additive effects, ultimately leading to transcriptional changes of the stem cells. Potential drivers of such changes in the epigenetic landscape of aged HSCs include proliferative history, DNA damage, and deregulation of key epigenetic enzymes and complexes. This review will focus largely on the two most characterized epigenetic marks - DNA methylation and histone modifications - but will also discuss the potential role of non-coding RNAs in regulating HSC function during aging.

Bellantuono, I., G. Sanguinetti, et al. "Progeroid syndromes: models for stem cell aging?" Biogerontology. 2012 Feb;13(1):63-75. doi: 10.1007/s10522-011-9347-2. Epub 2011 Jul 8.

Stem cells are responsible for tissue repair and maintenance and it is assumed that changes observed in the stem cell compartment with age underlie the concomitant decline in tissue function. Studies in murine models have highlighted the importance of intrinsic changes occurring in stem cells with age. They have also drawn the attention to other factors, such as changes in the local or systemic environment as the primary cause of stem cell dysfunction. Whilst knowledge in murine models has been advancing rapidly there has been little translation of these data to human aging. This is most likely due to the difficulties of testing the regenerative capacity of human stem cells in vivo and to substantial differences in the aging phenotype within humans. Here we summarize evidence to show how progeroid syndromes, integrated with other models, can be valuable tools in addressing questions about the role of stem cell aging in human degenerative diseases of older age and the molecular pathways involved.

Bersenev, A., K. Rozenova, et al. "Lnk deficiency partially mitigates hematopoietic stem cell aging." Aging Cell. 2012 Dec;11(6):949-59. doi: 10.1111/j.1474-9726.2012.00862.x. Epub 2012 Aug 27.

Upon aging, the number of hematopoietic stem cells (HSCs) in the bone marrow increases while their repopulation potential declines. Moreover, aged HSCs exhibit lineage bias in reconstitution experiments with an inclination toward myeloid at the expense of lymphoid potential. The adaptor protein Lnk is an important negative regulator of HSC homeostasis, as Lnk deficiency is associated with a 10-fold increase in HSC numbers in young mice. However, the age-related increase in functional HSC numbers found in wild-type HSCs was not observed in Lnk-deficient animals. Importantly, HSCs from aged Lnk null mice possess greatly enhanced self-renewal capacity and diminished exhaustion, as evidenced by serial transplant experiments. In addition, Lnk deficiency ameliorates the aging-associated lineage bias. Transcriptome analysis revealed that WT and Lnk-deficient HSCs share many aging-related changes in gene expression patterns. Nonetheless, Lnk null HSCs displayed altered expression of components in select signaling pathways with potential involvement in HSC self-renewal and aging. Taken together, these

results suggest that loss of Lnk partially mitigates age-related HSC alterations.

Chambers, S. M. and M. A. Goodell "Hematopoietic stem cell aging: wrinkles in stem cell potential." Stem Cell Rev. 2007 Fall;3(3):201-11.

Hematopoietic stem cells (HSC) continuously replenish the blood and immune systems. Their activity must be sustained throughout life to support optimal immune responses. It has been thought that stem cells may be somewhat protected from age because of their perpetual requirement to replenish the blood, however studies over the past 10 years have revealed dramatic changes in HSC function and phenotype with respect to age. When the number of HSC within murine bone marrow is measured, an increase in concentration and absolute number of HSC within the bone marrow is observed as the animal ages, paralleled with increased homogeneity of stem cell marker expression. Results from transplantation studies demonstrate that although there is a decline in hematopoietic output on a per-cell basis, the increase in number provides sufficient, yet abnormal, blood production throughout the lifespan of the animal. HSC may play a role in immunosenescence through cell-fate decisions leading to an overproduction of myeloid cells and an underproduction of lymphocytes. When examining gene expression of aged HSC, recent studies have highlighted several key factors contributing to increased inflammation, stress response and genomic instability. Here, we will review the general phenotype observed with aging of the hematopoietic system, focusing on the HSC, and compile recent expression profiling efforts that have examined HSC aging.

Dykstra, B. and G. de Haan "Hematopoietic stem cell aging and self-renewal." Cell Tissue Res. 2008 Jan;331(1):91-101. Epub 2007 Nov 16.

A functional decline of the immune system occurs during organismal aging that is attributable, in large part, to changes in the hematopoietic stem cell (HSC) compartment. In the mouse, several hallmark age-dependent changes in the HSC compartment have been identified, including an increase in HSC numbers, a decrease in homing efficiency, and a myeloid skewing of differentiation potential. Whether these changes are caused by gradual intrinsic changes within individual HSCs or by changes in the cellular composition of the HSC compartment remains unclear. However, of note, many of the aging properties of HSCs are highly dependent on their genetic background. In particular, the widely used C57Bl/6 strain appears to have unique HSC aging characteristics compared with those of other mouse strains. These differences can be exploited by using recombinant inbred strains to further our understanding of the genetic basis for HSC aging. The mechanism(s) responsible for HSC aging have only begun to be elucidated. Recent studies have reported co-ordinated variation in gene expression of HSCs with age, possibly as a result of epigenetic changes. In addition, an accumulation of DNA damage, in concert with an increase in intracellular reactive oxygen species, has been associated with aged HSCs. Nevertheless, whether age-related changes in HSCs are programmed to occur in a certain predictable fashion, or whether they are simply an accumulation of random changes over time remains unclear. Further, whether the genetic dysregulation observed in old HSCs is a cause or an effect of cellular aging is unknown.

Ergen, A. V. and M. A. Goodell "Mechanisms of hematopoietic stem cell aging." Exp Gerontol. 2010 Apr;45(4):286-90. doi: 10.1016/j.exger.2009.12.010. Epub 2009 Dec 23.

New blood cells are continually produced from the hematopoietic stem cells (HSCs) that reside in the bone marrow. Throughout the life-span of the organism, this stem cell reservoir sustains life. Although HSCs can persist in vivo longer than one life-span (Harrison et al., 1978), with aging, HSC regenerative potential diminishes and skewing from lymphopoiesis toward myelopoiesis occurs. The expansion in the HSC pool with aging provides sufficient, yet abnormal, blood production. Examination of gene expression changes in aged HSCs has provided a link between aging and genomic instability. Furthermore, studies on the effects of reactive oxygen species (ROS) on HSC aging has given more insight into the reasons for HSC failure. Understanding of the interactions between niche cells and HSCs and changes in them with aging, may give us insights into the lineage skewing phenotype observed in the aged, and also other immune dysfunctions.

Ertl, R. P., J. Chen, et al. "Effects of dietary restriction on hematopoietic stem-cell aging are genetically regulated." Blood. 2008 Feb 1;111(3):1709-16. Epub 2007 Oct 18.

Diminished stem-cell functions with age may be a major cause of anemias and other defects. Unfortunately, treatments that increase stem-cell function can also increase the incidence of cancers. Lifelong dietary restriction (DR) is known to decrease spontaneous cancers and lengthen lifespan. This study examines the effect of DR on the ability of bone marrow cells to repopulate irradiated recipients and produce erythrocytes and lymphocytes. In BALB/cByJ (BALB) mice, repopulating abilities decline with age;

DR ameliorates this trend. In C57BL/6J (B6) and (BALB x B6) F1 hybrid (F1) mice, repopulating abilities increase with age; DR maintains this increase. Hematopoietic stem cell (HSC) numbers are highly variable in aged BALB mice; however, the observed loss of marrow function results from a major loss in repopulating ability per HSC. DR greatly ameliorates this loss of function with age. In contrast, function per HSC in B6 mice is affected neither by age nor by DR. Thus, DR increases or maintains increased marrow repopulating ability with age in the 3 different genotypes tested, but effects on function per HSC depend on genotype. That DR increases or maintains stem-cell function with age, while decreasing cancer, has far-reaching health implications.

Fehrer, C. and G. Lepperdinger "Mesenchymal stem cell aging." Exp Gerontol. 2005 Dec;40(12):926-30. Epub 2005 Aug 25.

Stem cells are located throughout the adult body of higher organisms, supporting a continuous renewal and repair of tissues. Unique abilities of stem cells are self-renewal and multipotential differentiation. It is, therefore, of critical importance for an organism to maintain and control quantity and quality of stem cells within a given pool. Otherwise, when something goes awry within a stem cell, it is likely to have far-reaching effects. Mesenchymal stem cells (MSC) derived from various sources such as bone marrow or fat have been expanded in culture and differentiated in vitro into several lineages such as adipocytes, osteocytes or chondrocytes. In particular, aged human MSC show a decline in differentiation potential as well as in proliferation rate. The latter most likely reflects the fact that aged MSC suffer from eroded telomeres. Besides the individual age of the cell, stem and progenitor cell functions are influenced by the cellular environment, i.e. the niche and the architecture of the tissue, they reside in. This contribution reviews current knowledge about MSC aging (in vitro or in vivo), and respective difficulties for tissue engineering and stem cell therapy.

Flici, H. and A. Giangrande "Stem cell aging and plasticity in the Drosophila nervous system." Fly (Austin). 2012 Apr-Jun;6(2):108-12. doi: 10.4161/fly.19797. Epub 2012 Apr 1.

The majority of neural stem cells (NSCs) are considered as very plastic precursors that, in vitro, can divide indefinitely or differentiate into neurons or glia under specific conditions. However, in vivo, these cells actively proliferate during development, and later enter quiescence or apoptosis. This raises the issue as to whether stem cells keep their plastic behavior throughout their life, which may impact their therapeutic potential in regenerative medicine. Using the Gcm/Glide (for Glial cell missing/Glial cell deficient) transcription factor, which is able to trigger a complete and stable fate conversion into glia when ectopically expressed, we recently reported that the plasticity of Drosophila NSCs, commonly called neuroblasts (NBs), is age-dependent. When challenged with Gcm/Glide, newborn NBs are more easily converted into glia than old ones. Furthermore, the few old NBs that can be converted frequently generate cells with a stable (NB/glia) intermediate identity, a phenotype characteristic of cancer cells. We here discuss the concept of aging in NSC fate conversion and speculate on how our findings impact the ongoing debate concerning NSC plasticity.

Florian, M. C., K. Dorr, et al. "Cdc42 activity regulates hematopoietic stem cell aging and rejuvenation." Cell Stem Cell. 2012 May 4;10(5):520-30. doi: 10.1016/j.stem.2012.04.007.

The decline in hematopoietic function seen during aging involves a progressive reduction in the immune response and an increased incidence of myeloid malignancy, and has been linked to aging of hematopoietic stem cells (HSCs). The molecular mechanisms underlying HSC aging remain unclear. Here we demonstrate that elevated activity of the small RhoGTPase Cdc42 in aged HSCs is causally linked to HSC aging and correlates with a loss of polarity in aged HSCs. Pharmacological inhibition of Cdc42 activity functionally rejuvenates aged HSCs, increases the percentage of polarized cells in an aged HSC population, and restores the level and spatial distribution of histone H4 lysine 16 acetylation to a status similar to that seen in young HSCs. Our data therefore suggest a mechanistic role for Cdc42 activity in HSC biology and epigenetic regulation, and identify Cdc42 activity as a pharmacological target for ameliorating stem cell aging.

Fujimaki, S., T. Wakabayashi, et al. "The regulation of stem cell aging by Wnt signaling." Histol Histopathol. 2015 Aug 31:11657.

Aging is an inevitable physiological process that leads to the dysfunction of various tissues, and these changes may contribute to certain diseases, and ultimately death. Recent research has discovered biological pathways that promote aging. This review focuses on Wnt signaling, Wnt is a highly conserved secreted signaling molecule that plays an essential role in the development and function of various tissues, and is a notable factor that regulates aging. Although Wnt signaling influences aging in various tissues, its effects are particularly prominent in neuronal tissue and skeletal muscle. In neuronal tissue, neurogenesis is attenuated by the downregulation of Wnt signaling with aging. Skeletal muscle can also become weaker

with aging, in a process known as sarcopenia. A notable cause of sarcopenia is the myogenic-to-fibrogenic trans-differentiation of satellite cells by excessive upregulation of Wnt signaling with aging, resulting in the impaired regenerative capacity of aged skeletal muscle. However, exercise is very useful for preventing the age-related alterations in neuronal tissue and skeletal muscle. Upregulation of Wnt signaling is implicated in the positive effects of exercise, resulting in the activation of neurogenesis in adult neuronal tissue and myogenesis in mature skeletal muscle. Although more investigations are required to thoroughly understand age-related changes and their biological mechanisms in a variety of tissues, this review proposes exercise as a useful therapy for the elderly, to prevent the negative effects of aging and maintain their quality of life.

Fujita, K. and N. Tsumaki "[Stem cell aging and the implications for stem cell-based therapies for aging-related diseases and aged tissues]." Clin Calcium. 2013 Jan;23(1):65-73. doi: CliCa13016573.

Adult stem cells exist in most mammalian tissues to maintain their homeostasis and help repair them. Reductions in adult stem cell function and/or number are clearly associated with aging, however, the causal correlations between such findings and the effects of aging are largely unknown. Some stem cell functional changes, such as the loss of lineage specificity and self-renewal capacity, senescence and transformation, arise in stem cells autonomously during the aging process. These autonomous changes of stem cell functions reflect the damaging effects of age on the genome, epigenome, and proteome. Other stem cell functional changes are influenced by the age-related changes in the local microenvironments (niches) or systemic environments. If stem cell-based therapy can be used not only for age-related degenerative diseases, but also normal functional declines associated with aging, consideration of the behavior of stem cells based on effects from the local microenvironments (niches) and systemic environments in older individuals will therefore be needed.

Fuller, J. "Stem cell aging and cancer." Sci Aging Knowledge Environ. 2006 May 24;2006(9):pe12.

Stem cells are capable of self-renewal, differentiation into various lineages, and proliferation; thus, they play critical roles in the functioning and maintenance of many biological systems. However, these unique qualities of stem cells also make them more vulnerable to mutations as the organism ages. The biggest risk factor in cancer development is age, and most scientists believe that cancers partly result from a buildup of mutations in different cell types over time. This accumulation of mutations takes place over the course of a person's lifetime, during which repeated rounds of cell division result in editing errors in the DNA. Genetic alterations can cause changes in the signaling pathways controlling proliferation, differentiation, and apoptosis. In the case of stem cells, such mutations would be passed on to all of the stem cell's progeny, ultimately resulting in a pool of stem cells that feeds neoplastic formation. Studies aiming to identify and characterize these putative cancer stem cells and to understand how they arise will shed light on the process of stem cell aging and its role in cancer.

Geiger, H. and Y. Zheng "Regulation of hematopoietic stem cell aging by the small RhoGTPase Cdc42." Exp Cell Res. 2014 Dec 10;329(2):214-9. doi: 10.1016/j.yexcr.2014.09.001. Epub 2014 Sep 16.

Aging of stem cells might be the underlying cause of tissue aging in tissue that in the adult heavily rely on stem cell activity, like the blood forming system. Hematopoiesis, the generation of blood forming cells, is sustained by hematopoietic stem cells. In this review article, we introduce the canonical set of phenotypes associated with aged HSCs, focus on the novel aging-associated phenotype apolarity caused by elevated activity of the small RhoGTPase in aged HSCs, discuss the role of Cdc42 in hematopoiesis and describe that pharmacological inhibition of Cdc42 activity in aged HSCs results in functionally young and thus rejuvenated HSCs.

Kasper, G., L. Mao, et al. "Insights into mesenchymal stem cell aging: involvement of antioxidant defense and actin cytoskeleton." Stem Cells. 2009 Jun;27(6):1288-97. doi: 10.1002/stem.49.

Progenitor cells such as mesenchymal stem cells (MSCs) have elicited great hopes for therapeutic augmentation of physiological regeneration processes, e.g., for bone fracture healing. However, regeneration potential decreases with age, which raises questions about the efficiency of autologous approaches in elderly patients. To elucidate the mechanisms and cellular consequences of aging, the functional and proteomic changes in MSCs derived from young and old Sprague-Dawley rats were studied concurrently. We demonstrate not only that MSC concentration in bone marrow declines with age but also that their function is altered, especially their migratory capacity and susceptibility toward senescence. High-resolution two-dimensional electrophoresis of the MSC proteome, under conditions of in vitro self-renewal as well as osteogenic stimulation, identified several age-dependent proteins, including members of the calponin protein family as well as galectin-3. Functional annotation clustering revealed that age-affected molecular functions are associated with cytoskeleton

organization and antioxidant defense. These proteome screening results are supported by lower actin turnover and diminished antioxidant power in aged MSCs, respectively. Thus, we postulate two main reasons for the compromised cellular function of aged MSCs: (a) declined responsiveness to biological and mechanical signals due to a less dynamic actin cytoskeleton and (b) increased oxidative stress exposure favoring macromolecular damage and senescence. These results, along with the observed similar differentiation potentials, imply that MSC-based therapeutic approaches for the elderly should focus on attracting the cells to the site of injury and oxidative stress protection, rather than merely stimulating differentiation.

Kikushige, Y. and T. Miyamoto "Hematopoietic stem cell aging and chronic lymphocytic leukemia pathogenesis." Int J Hematol. 2014 Oct;100(4):335-40. doi: 10.1007/s12185-014-1651-6. Epub 2014 Aug 7.

Human malignancies develop through the multistep acquisition of critical somatic mutations during the clinical course. Regarding hematological malignancies, recent novel findings have indicated that hematopoietic stem cells (HSCs), which have the potential to self-renew and differentiate into multilineage hematopoietic cells, are an important cellular target for the accumulation of critical somatic mutations and play a central role in myeloid malignancy development. In contrast to myeloid malignancies, mature lymphoid malignancies, such as chronic lymphocytic leukemia (CLL), are considered to directly originate from differentiated mature lymphocytes; however, we previously reported that the propensity to generate clonal B cells had already been acquired at the HSC stage in CLL patients. Similarly, HSC involvement has been reported in the pathogenesis of mature T cell lymphomas. These studies indicate that, in mature lymphoid, if not all, malignancies, HSCs should be considered as the critical cellular target in the oncogenic process. The prevalence of these hematological malignancies dramatically increases with age, and the effect of aging HSCs should thus be taken into account when investigating the stepwise malignant transformation process of these age-associated malignancies.

Klauke, K. and G. de Haan "Polycomb group proteins in hematopoietic stem cell aging and malignancies." Int J Hematol. 2011 Jul;94(1):11-23. doi: 10.1007/s12185-011-0857-0. Epub 2011 Apr 27.

Protection of the transcriptional "stemness" network is important to maintain a healthy hematopoietic stem cells (HSCs) compartment during the lifetime of the organism. Recent evidence shows that fundamental changes in the epigenetic status of HSCs might be one of the driving forces behind many age-related HSC changes and might pave the way for HSC malignant transformation and subsequent leukemia development, the incidence of which increases exponentially with age. Polycomb group (PcG) proteins are key epigenetic regulators of HSC cellular fate decisions and are often found to be misregulated in human hematopoietic malignancies. In this review, we speculate that PcG proteins balance HSC aging against the risk of developing cancer, since a disturbance in PcG genes and proteins affects several important cellular processes such as cell fate decisions, senescence, apoptosis, and DNA damage repair.

Lepperdinger, G. "Inflammation and mesenchymal stem cell aging." Curr Opin Immunol. 2011 Aug;23(4):518-24. doi: 10.1016/j.coi.2011.05.007. Epub 2011 Jun 22.

In adults, mesenchymal stromal cells contain tissue-specific multipotent stem cells, MSC, which can be found throughout the body. With advancing age, tight controls of regulatory networks, which guide MSC biology, gradually deteriorate. Aberrations within the MSC microenvironment such as chronic inflammation eventually lead to adverse manifestations, such as the accumulation of fat deposits in bone and muscles, impaired healing and fibrosis after severe injury, or altered hematopoiesis and autoimmunity. MSC can also specifically interact with a large variety of immune cells, and in doing so, they secrete cytoprotective and immunoregulatory molecules, which together with intercellular contacts mediate immune modulatory processes. This review comprehends the current knowledge regarding molecular mechanisms and cellular interactions that occur in stem cell niches, which are jointly shared between MSC and hematopoietic stem and progenitor cells, as well as those intracellular interdependences taking place between mesenchymal and a wide variety of hematopoietic progeny in particular T lymphocytes, which eventually perturb tissue homeostasis and immunology at advanced age.

Madonna, R., F. B. Engel, et al. "Stem Cell Aging and Age-Related Cardiovascular Disease: Perspectives of Treatment by Ex-vivo Stem Cell Rejuvenation." Curr Drug Targets. 2015;16(8):780-5.

Aging affects endogenous stem cells in terms of functionality and numbers. In particular, during aging, the stemness property can decrease because of enhanced apoptotic cell death and senescence. In addition, aging and aging-related co-morbidities affect the paracrine activity of stem cells and the efficiency of their transplantation. Collectively, this leads to a reduction of the capacity of organs to repair themselves, possibly due to a reduced functional

capability of stem cells. Therefore, major efforts have been invested to improve the repair capability of stem cells in aged individuals by overexpressing antisenescence and antiapoptotic genes. In this review, we describe critical genes and signaling pathways in stem cell aging and discuss ex vivo genetic modification approaches aimed at stem cell rejuvenation that are of interest for the cardiovascular system.

Mantel, C. and H. E. Broxmeyer "Sirtuin 1, stem cells, aging, and stem cell aging." Curr Opin Hematol. 2008 Jul;15(4):326-31. doi: 10.1097/MOH.0b013e3283043819.

PURPOSE OF REVIEW: New discoveries focused on mitochondrial metabolism and gene silencing and their regulation by the sirtuin family of protein deacetylases is stimulating new ideas on how to improve geriatric medicine. Information about sertuins in stem cell biology is scarce. We consider recent information on sirtuin 1, its role in aging and metabolism in several species and tissues, and attempt to anticipate how it might influence stem cell aging. RECENT FINDINGS: Calorie restriction lengthens lifespan, in part, due to mitochondrial metabolism reorganization through sirtuin 1/peroxisome proliferator-activated receptor gamma-coactivator-1alpha-regulated mitochondrial biogenesis. This reduces radical oxygen species levels that cause macromolecule damage, a major contributor to aging. Little is known about these processes in stem cells, whose longevity is implicated in human aging. Recent work indicates that sirtuin 1 influences growth-factor responses and maintenance of stem cells. Sirtuin 1 is required for calorie restriction-induced lifespan extension in mice, and calorie restriction upregulates sirtuin 1 in humans. Sirtuin 1 also appears to influence lineage/cell-fate decisions of stem cells via redox status. SUMMARY: The same thermodynamic and biochemical mechanisms linked to aging in somatic cells may also work in stem cells. Developments in mitochondrial biology and new drug development based on this knowledge are finding their way into the clinic (i.e. diabetes) and may illuminate new ways of manipulating and using stem cells in medicine.

Minamino, T. and I. Komuro "Vascular aging: insights from studies on cellular senescence, stem cell aging, and progeroid syndromes." Nat Clin Pract Cardiovasc Med. 2008 Oct;5(10):637-48. doi: 10.1038/ncpcardio1324. Epub 2008 Sep 2.

Epidemiological studies have shown that age is the chief risk factor for atherosclerotic cardiovascular diseases, but the molecular mechanisms that underlie the increase in risk conferred by aging remain unclear. Evidence suggests that the cardiovascular repair system is impaired with advancing age, thereby inducing age-associated cardiovascular dysfunction. Such impairment could be attributable to senescence of cardiovascular tissues at the cellular level as a result of telomere shortening, DNA damage, and genomic instability. In fact, the replicative ability of cardiovascular cells, particularly stem cells and/or progenitor cells, has been shown to decline with age. Recently, considerable progress has been made in understanding the pathogenesis of human progeroid syndromes that feature cardiovascular aging. Most of the genes responsible have a role in DNA metabolism, and mutated forms of these genes result in alterations of the response to DNA damage and in decreased cell proliferation, which might be common features of a phenotype of aging. Here we review the cardiovascular research on cellular senescence, stem cell aging, and progeroid syndromes and discuss the potential role of cellular senescence in the mechanisms underlying both normal aging and premature aging syndromes.

Mohrin, M., J. Shin, et al. "Stem cell aging. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging." Science. 2015 Mar 20;347(6228):1374-7. doi: 10.1126/science.aaa2361.

Deterioration of adult stem cells accounts for much of aging-associated compromised tissue maintenance. How stem cells maintain metabolic homeostasis remains elusive. Here, we identified a regulatory branch of the mitochondrial unfolded protein response (UPR(mt)), which is mediated by the interplay of SIRT7 and NRF1 and is coupled to cellular energy metabolism and proliferation. SIRT7 inactivation caused reduced quiescence, increased mitochondrial protein folding stress (PFS(mt)), and compromised regenerative capacity of hematopoietic stem cells (HSCs). SIRT7 expression was reduced in aged HSCs, and SIRT7 up-regulation improved the regenerative capacity of aged HSCs. These findings define the deregulation of a UPR(mt)-mediated metabolic checkpoint as a reversible contributing factor for HSC aging.

Muller-Sieburg, C. and H. B. Sieburg "Stem cell aging: survival of the laziest?" Cell Cycle. 2008 Dec 15;7(24):3798-804. Epub 2008 Dec 16.

The question whether stem cells age remains an enigma. Traditionally, aging was thought to change the properties of hematopoietic stem cells (HSC). We discuss here a new model of stem cell aging that challenges this view. It is now well-established that the HSC compartment is heterogeneous, consisting of epigenetically fixed subpopulations of HSC that differ in self-renewal and differentiation capacity. New data

show that the representation of these HSC subsets changes during aging. HSC that generate lymphocyte-rich progeny are depleted, while myeloid-biased HSC are enriched in the aged HSC compartment. Myeloid-biased HSC, even when isolated from young donors, have most of the characteristics that had been attributed to aged HSC. Thus, the distinct behavior of the HSC isolated from aged hosts is due to the accumulation of myeloid-biased HSC. By extension this means that the properties of individual HSC are not substantially changed during the lifespan of the organism and that aged hosts do not contain many aged HSC. Myeloid-biased HSC give rise to mature cells slowly but contribute for a long time to peripheral hematopoiesis. We propose that such slow, "lazy" HSC are less likely to be transformed and therefore may safely sustain hematopoiesis for a long time.

Noda, S., H. Ichikawa, et al. "Hematopoietic stem cell aging is associated with functional decline and delayed cell cycle progression." Biochem Biophys Res Commun. 2009 May 29;383(2):210-5. doi: 10.1016/j.bbrc.2009.03.153. Epub 2009 Apr 5.

The molecular mechanisms underlying hematopoietic stem cell (HSC) aging remain to be elucidated. In this study, we investigated age-related changes in the functional and phenotypic properties of murine HSCs. Consistent with previous studies, we found that the number and frequency of CD34(-/low)c-Kit(+)Sca-1(+)lineage marker(-) (CD34(-)KSL) cells, a highly enriched HSC population, significantly increased in old mice, though their repopulating ability was reduced. Continuous bromodeoxyuridine labeling revealed a significant delay in the cell cycle progression of CD34(-)KSL cells in old mice. This delay was also observed in young recipients transplanted with whole bone marrow cells from old mice. When cultured in vitro, CD34(-)KSL cells from old mice showed a greater capacity to give rise to primitive CD48(-)KSL cells with reduced HSC activity. Gene expression profiling identified age-related changes in the expression of several cell cycle regulatory genes, including p21/Cdkn1a and p18/Cdkn2c. These results support the notion that HSC aging is largely regulated by an intrinsic genetic program.

Norddahl, G. L., C. J. Pronk, et al. "Accumulating mitochondrial DNA mutations drive premature hematopoietic aging phenotypes distinct from physiological stem cell aging." Cell Stem Cell. 2011 May 6;8(5):499-510. doi: 10.1016/j.stem.2011.03.009.

Somatic stem cells mediate tissue maintenance for the lifetime of an organism. Despite the well-established longevity that is a prerequisite for such function, accumulating data argue for compromised stem cell function with age. Identifying the mechanisms underlying age-dependent stem cell dysfunction is therefore key to understanding the aging process. Here, using a model carrying a proofreading-defective mitochondrial DNA polymerase, we demonstrate hematopoietic defects reminiscent of premature HSC aging, including anemia, lymphopenia, and myeloid lineage skewing. However, in contrast to physiological stem cell aging, rapidly accumulating mitochondrial DNA mutations had little functional effect on the hematopoietic stem cell pool, and instead caused distinct differentiation blocks and/or disappearance of downstream progenitors. These results show that intact mitochondrial function is required for appropriate multilineage stem cell differentiation, but argue against mitochondrial DNA mutations per se being a primary driver of somatic stem cell aging.

Oh, J., Y. D. Lee, et al. "Stem cell aging: mechanisms, regulators and therapeutic opportunities." Nat Med. 2014 Aug;20(8):870-80. doi: 10.1038/nm.3651.

Aging tissues experience a progressive decline in homeostatic and regenerative capacities, which has been attributed to degenerative changes in tissue-specific stem cells, stem cell niches and systemic cues that regulate stem cell activity. Understanding the molecular pathways involved in this age-dependent deterioration of stem cell function will be critical for developing new therapies for diseases of aging that target the specific causes of age-related functional decline. Here we explore key molecular pathways that are commonly perturbed as tissues and stem cells age and degenerate. We further consider experimental evidence both supporting and refuting the notion that modulation of these pathways per se can reverse aging phenotypes. Finally, we ask whether stem cell aging establishes an epigenetic 'memory' that is indelibly written or one that can be reset.

Ortells, M. C. and W. M. Keyes "New insights into skin stem cell aging and cancer." Biochem Soc Trans. 2014 Jun;42(3):663-9. doi: 10.1042/BST20140045.

Adult tissue homoeostasis requires continual replacement of cells that are lost due to normal turnover, injury and disease. However, aging is associated with an overall decline in tissue function and homoeostasis, suggesting that the normal regulatory processes that govern self-renewal and regeneration may become impaired with age. Tissue-specific SCs (stem cells) lie at the apex of organismal conservation and regeneration, ultimately being responsible for continued tissue maintenance. In many tissues, there are changes in SC numbers, or alteration of their growth properties during aging, often

involving imbalances in tumour-suppressor- and oncogene-mediated pathways. Uncovering the molecular mechanisms leading to changes in SC function during aging will provide an essential tool to address tissue-specific age-related pathologies. In the present review, we summarize the age-related alterations found in different tissue SC populations, highlighting recently identified changes in aged HFSCs (hair-follicle SCs) in the skin.

Oshima, M. and A. Iwama "Epigenetics of hematopoietic stem cell aging and disease." Int J Hematol. 2014 Oct;100(4):326-34. doi: 10.1007/s12185-014-1647-2. Epub 2014 Aug 1.

The decline in the regenerative potential of tissues is one of the most evident characteristics of aging. Stem cell aging determines the aging phenotypes of tissues, and has thus been recognized as one of the hallmarks of mammalian aging. An emerging body of evidence supports an essential role for epigenetic controls in regulating cellular functions. Many epigenetic modifications become stabilized at a particular stage of development. However, epigenetic marks can also readily change over time. This "epigenetic drift" contributes to changes in cellular phenotypes and when it takes place in adult stem cells, may play an important role in stem cell aging. Epigenetic alterations are now recognized as another hallmark of mammalian aging. This process depends on cell intrinsic and extrinsic factors, although the underlying molecular mechanisms remain largely unknown. Here, we review the current progress in the study of epigenetic changes regulating aging hematopoietic stem cells (HSCs). We particularly focus on the epigenome and its regulators in aging HSCs.

Pan, L., S. Chen, et al. "Stem cell aging is controlled both intrinsically and extrinsically in the Drosophila ovary." Cell Stem Cell. 2007 Oct 11;1(4):458-69. doi: 10.1016/j.stem.2007.09.010.

It is widely postulated that tissue aging could be, at least partially, caused by reduction of stem cell number, activity, or both. However, the mechanisms of controlling stem cell aging remain largely a mystery. Here, we use Drosophila ovarian germline stem cells (GSCs) as a model to demonstrate that age-dependent decline in the functions of stem cells and their niche contributes to overall stem cell aging. BMP signaling activity from the niche significantly decreases with age, and increasing BMP signaling can prolong GSC life span and promote their proliferation. In addition, the age-dependent E-cadherin decline in the stem cell-niche junction also contributes to stem cell aging. Finally, overexpression of SOD, an enzyme that helps eliminate free oxygen species, in either GSCs or their niche alone can prolong GSC life span and increase GSC proliferation. Therefore, this study demonstrates that stem cell aging is controlled extrinsically and intrinsically in the Drosophila ovary.

Przybilla, J., J. Galle, et al. "Is adult stem cell aging driven by conflicting modes of chromatin remodeling?" Bioessays. 2012 Oct;34(10):841-8. doi: 10.1002/bies.201100190. Epub 2012 Jul 23.

Epigenetic control of gene expression by chromatin remodeling is critical for adult stem cell function. A decline in stem cell function is observed during aging, which is accompanied by changes in the chromatin structure that are currently unexplained. Here, we hypothesize that these epigenetic changes originate from the limited cellular capability to inherit epigenetic information. We suggest that spontaneous loss of histone modification, due to fluctuations over short time scales, gives rise to long-term changes in DNA methylation and, accordingly, in gene expression. These changes are assumed to impair stem cell function and, thus, to contribute to aging. We discuss cell replication as a major source of fluctuations in histone modification patterns. Gene silencing by our proposed mechanism can be interpreted as a manifestation of the conflict between the stem cell plasticity required for tissue regeneration and the permanent silencing of potentially deleterious genomic sequences.

Reitinger, S., M. Schimke, et al. "Systemic impact molds mesenchymal stromal/stem cell aging." Transfus Apher Sci. 2015 Jun;52(3):285-9. doi: 10.1016/j.transci.2015.04.008. Epub 2015 Apr 8.

Aging is associated with an accruing emergence of non-functional tissues. Mesenchymal stem cells (MSC) bring forth progenitors with multi-lineage differentiation potential, yet, they also exhibit anti-inflammatory and tissue-protective properties. Due to aging, altered tissue microenvironments constrict controlled stem cell proliferation and progenitor differentiation, thus diminishing the fitness of MSC. Therefore, deepening our understanding of metabolic, molecular and environmental factors impacting on MSC during human aging as well as providing new vistas on their role in promoting healthy aging and preventing age-associated disease is pivot. It is anticipated that integrative quantification of systemic parameters dominantly impacting on MSC will also enable effective personalized prognosis and provision of effective early medical interventions. Working along this line, it can be envisaged that standards in medical therapies can be individually adjusted by accounting not solely for the patient's chronological age or other physical parameters rather than specific physiological parameters which are

believed to functionally shape stem cell niches within the bone marrow.

Rossi, D. J., D. Bryder, et al. "Hematopoietic stem cell aging: mechanism and consequence." Exp Gerontol. 2007 May;42(5):385-90. Epub 2007 Jan 31.

Advancing age is frequented by the onset of a variety of hematological conditions characterized by diminished homeostatic control of blood cell production. The fact that upstream hematopoietic stem and progenitor cells are obligate mediators of homeostatic control of all blood lineages, has implicated the involvement of these cells in the pathophysiology of these conditions. Indeed, evidence from our group and others has suggested that two of the most clinically significant age-associated hematological conditions, namely, the diminution of the adaptive immune system and the elevated incidence of myeloproliferative diseases, have their origin in cell autonomous changes in the functional capacity of hematopoietic stem cells.

Rossi, D. J., D. Bryder, et al. "Cell intrinsic alterations underlie hematopoietic stem cell aging." Proc Natl Acad Sci U S A. 2005 Jun 28;102(26):9194-9. Epub 2005 Jun 20.

Loss of immune function and an increased incidence of myeloid leukemia are two of the most clinically significant consequences of aging of the hematopoietic system. To better understand the mechanisms underlying hematopoietic aging, we evaluated the cell intrinsic functional and molecular properties of highly purified long-term hematopoietic stem cells (LT-HSCs) from young and old mice. We found that LT-HSC aging was accompanied by cell autonomous changes, including increased stem cell self-renewal, differential capacity to generate committed myeloid and lymphoid progenitors, and diminished lymphoid potential. Expression profiling revealed that LT-HSC aging was accompanied by the systemic down-regulation of genes mediating lymphoid specification and function and up-regulation of genes involved in specifying myeloid fate and function. Moreover, LT-HSCs from old mice expressed elevated levels of many genes involved in leukemic transformation. These data support a model in which age-dependent alterations in gene expression at the stem cell level presage downstream developmental potential and thereby contribute to age-dependent immune decline, and perhaps also to the increased incidence of leukemia in the elderly.

Rota, M., N. LeCapitaine, et al. "Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66shc gene." Circ Res. 2006 Jul 7;99(1):42-52. Epub 2006 Jun 8.

Diabetes leads to a decompensated myopathy, but the etiology of the cardiac disease is poorly understood. Oxidative stress is enhanced with diabetes and oxygen toxicity may alter cardiac progenitor cell (CPC) function resulting in defects in CPC growth and myocyte formation, which may favor premature myocardial aging and heart failure. We report that in a model of insulin-dependent diabetes mellitus, the generation of reactive oxygen species (ROS) leads to telomeric shortening, expression of the senescent associated proteins p53 and p16INK4a, and apoptosis of CPCs, impairing the growth reserve of the heart. However, ablation of the p66shc gene prevents these negative adaptations of the CPC compartment, interfering with the acquisition of the heart senescent phenotype and the development of heart failure with diabetes. ROS elicit 3 cellular reactions: low levels activate cell growth, intermediate quantities trigger cell apoptosis, and high amounts initiate cell necrosis. CPC replication predominates in diabetic p66shc-/-, whereas CPC apoptosis and myocyte apoptosis and necrosis prevail in diabetic wild type. Expansion of CPCs and developing myocytes preserves cardiac function in diabetic p66shc-/-, suggesting that intact CPCs can effectively counteract the impact of uncontrolled diabetes on the heart. The recognition that p66shc conditions the destiny of CPCs raises the possibility that diabetic cardiomyopathy is a stem cell disease in which abnormalities in CPCs define the life and death of the heart. Together, these data point to a genetic link between diabetes and ROS, on the one hand, and CPC survival and growth, on the other.

So, A. Y., J. W. Jung, et al. "DNA methyltransferase controls stem cell aging by regulating BMI1 and EZH2 through microRNAs." PLoS One. 2011 May 10;6(5):e19503. doi: 10.1371/journal.pone.0019503.

Epigenetic regulation of gene expression is well known mechanism that regulates cellular senescence of cancer cells. Here we show that inhibition of DNA methyltransferases (DNMTs) with 5-azacytidine (5-AzaC) or with specific small interfering RNA (siRNA) against DNMT1 and 3b induced the cellular senescence of human umbilical cord blood-derived multipotent stem cells (hUCB-MSCs) and increased p16(INK4A) and p21(CIP1/WAF1) expression. DNMT inhibition changed histone marks into the active forms and decreased the methylation of CpG islands in the p16(INK4A) and p21(CIP1/WAF1) promoter regions. Enrichment of EZH2, the key factor that methylates histone H3 lysine 9 and 27 residues, was decreased on the p16(INK4A) and p21(CIP1/WAF1) promoter regions. We found that DNMT inhibition decreased expression levels of Polycomb-group (PcG) proteins and increased expression of microRNAs (miRNAs),

which target PcG proteins. Decreased CpG island methylation and increased levels of active histone marks at genomic regions encoding miRNAs were observed after 5-AzaC treatment. Taken together, DNMTs have a critical role in regulating the cellular senescence of hUCB-MSCs through controlling not only the DNA methylation status but also active/inactive histone marks at genomic regions of PcG-targeting miRNAs and p16(INK4A) and p21(CIP1/WAF1) promoter regions.

Song, Z., Z. Ju, et al. "Cell intrinsic and extrinsic mechanisms of stem cell aging depend on telomere status." Exp Gerontol. 2009 Jan-Feb;44(1-2):75-82. doi: 10.1016/j.exger.2008.06.009. Epub 2008 Jul 3.

The function of adult stem cells declines during aging and chronic diseases. An understanding of the molecular mechanisms underlying these processes will help to identify targets for future therapies in order to improve regenerative reserve and organ maintenance. Telomere shortening represents a cell intrinsic mechanism inducing DNA damage in aging cells. Current studies in telomerase knockout mice have shown that telomere dysfunction induces cell intrinsic checkpoints and environmental alteration that limit stem cell function. While these phenotypes differ from wild-type mice with long telomere reserves, they appear to be relevant for human aging, which is associated with an accumulation of telomere dysfunction and DNA damage.

Sousa-Victor, P., L. Garcia-Prat, et al. "Muscle stem cell aging: regulation and rejuvenation." Trends Endocrinol Metab. 2015 Jun;26(6):287-96. doi: 10.1016/j.tem.2015.03.006. Epub 2015 Apr 10.

Aging is characterized by a progressive decline of physiological integrity leading to the loss of tissue function and vulnerability to disease, but its causes remain poorly understood. Skeletal muscle has an outstanding regenerative capacity that relies on its resident stem cells (satellite cells). This capacity declines with aging, and recent discoveries have redefined our view of why this occurs. Here, we discuss how an interconnection of extrinsic changes in the systemic and local environment and cell-intrinsic mechanisms might provoke failure of normal muscle stem cell functions with aging. We focus particularly on the emergent biology of rejuvenation of old satellite cells, including cells of geriatric age, by restoring traits of youthfulness, with the final goal of improving human health during aging.

Van Zant, G. and Y. Liang "Concise review: hematopoietic stem cell aging, life span, and transplantation." Stem Cells Transl Med. 2012 Sep;1(9):651-7. doi: 10.5966/sctm.2012-0033. Epub 2012 Sep 5.

Self-renewal and multilineage differentiation of stem cells are keys to the lifelong homeostatic maintenance of tissues and organs. Hematopoietic aging, characterized by immunosenescence, proinflammation, and anemia, is attributed to age-associated changes in the number and function of hematopoietic stem cells (HSCs) and their microenvironmental niche. Genetic variants and factors regulating stem cell aging are correlatively or causatively associated with overall organismal aging and longevity. Translational use of HSCs for transplantation and gene therapy demands effective methods for stem cell expansion. Targeting the molecular pathways involved in HSC self-renewal, proliferation, and homing has led to enhanced expansion and engraftment of stem cells upon transplantation. HSC transplantation is less effective in elderly people, even though this is the demographic with the greatest need for this form of treatment. Thus, understanding the biological changes in the aging of stem cells as well as local and systematic environments will improve the efficacy of aged stem cells for regenerative medicine and ultimately facilitate improved health and life spans.

Wahlestedt, M., G. L. Norddahl, et al. "An epigenetic component of hematopoietic stem cell aging amenable to reprogramming into a young state." Blood. 2013 May 23;121(21):4257-64. doi: 10.1182/blood-2012-11-469080. Epub 2013 Mar 8.

Aging of hematopoietic stem cells (HSCs) leads to several functional changes, including alterations affecting self-renewal and differentiation. Although it is well established that many of the age-induced changes are intrinsic to HSCs, less is known regarding the stability of this state. Here, we entertained the hypothesis that HSC aging is driven by the acquisition of permanent genetic mutations. To examine this issue at a functional level in vivo, we applied induced pluripotent stem (iPS) cell reprogramming of aged hematopoietic progenitors and allowed the resulting aged-derived iPS cells to reform hematopoiesis via blastocyst complementation. Next, we functionally characterized iPS-derived HSCs in primary chimeras and after the transplantation of re-differentiated HSCs into new hosts, the gold standard to assess HSC function. Our data demonstrate remarkably similar functional properties of iPS-derived and endogenous blastocyst-derived HSCs, despite the extensive chronological and proliferative age of the former. Our results, therefore, favor a model in which an underlying, but reversible, epigenetic component is a hallmark of HSC aging.

Wahlestedt, M., C. J. Pronk, et al. "Concise review: hematopoietic stem cell aging and the prospects for rejuvenation." Stem Cells Transl Med. 2015 Feb;4(2):186-94. doi: 10.5966/sctm.2014-0132. Epub 2014 Dec 29.

Because of the continuous increases in lifetime expectancy, the incidence of age-related diseases will, unless counteracted, represent an increasing problem at both the individual and socioeconomic levels. Studies on the processes of blood cell formation have revealed several shortcomings as a consequence of chronological age. They include a reduced ability to mount adaptive immune responses and a blood cell composition skewed toward myeloid cells, with the latter coinciding with a dramatically increased incidence of myelogenous diseases, including cancer. Conversely, the dominant forms of acute leukemia affecting children associate with the lymphoid lineages. A growing body of evidence has suggested that aging of various organs and cellular systems, including the hematopoietic system, associates with a functional demise of tissue-resident stem cell populations. Mechanistically, DNA damage and/or altered transcriptional landscapes appear to be major drivers of the hematopoietic stem cell aging state, with recent data proposing that stem cell aging phenotypes are characterized by at least some degree of reversibility. These findings suggest the possibility of rejuvenating, or at least dampening, stem cell aging phenotypes in the elderly for therapeutic benefit.

Waskar, M., Y. Li, et al. "Stem cell aging in the Drosophila ovary." Age (Dordr). 2005 Sep;27(3):201-12. doi: 10.1007/s11357-005-2914-1. Epub 2005 Dec 31.

Accumulating evidence suggests that with time human stem cells may become defective or depleted, thereby contributing to aging and aging-related diseases. Drosophila provides a convenient model system in which to study stem cell aging. The adult Drosophila ovary contains two types of stem cells: the germ-line stem cells give rise to the oocyte and its supporting nurse cells, while the somatic stem cells give rise to the follicular epithelium-a highly differentiated tissue that surrounds each oocyte as it develops. Genetic and transgenic analyses have identified several conserved signaling pathways that function in the ovary to regulate stem cell maintenance, division and differentiation, including the wingless, hedgehog, JAK/STAT, insulin and TGF-beta pathways. During Drosophila aging the division of the stem cells decreases dramatically, coincident with reduced egg production. It is unknown if this reproductive senescence is due to a defect in the stem cells themselves, or due to the lack of signals normally sent to the stem cells from elsewhere in the animal, such as from the central nervous system or the stem cell niche. Methods are being developed to genetically mark stem cells in adult Drosophila and measure their survival, division rate and function during aging.

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